(including steroid-resistant asthma), asbestosis, and silicosis (De Nardo et al., Am. J. Pathol., 184: 42-54, 2014 and Kim et al. Am J Respir Crit Care Med. 2017 196(3): 283-97). Furthermore, NLRP3 has a role in the development of liver disease, kidney disease and aging. Many of these associations were defined using *Nlrp3*$^{-/-}$ mice, but there have also been insights into the specific activation of NLRP3 in these diseases. In type 2 diabetes mellitus (T2D), the deposition of islet amyloid polypeptide in the pancreas activates NLRP3 and IL-1β signalling, resulting in cell death and inflammation.

Several small molecules have been shown to inhibit the NLRP3 inflammasome. Glyburide inhibits IL-1β production at micromolar concentrations in response to the activation of NLRP3 but not NLRC4 or NLRP1. Other previously characterised weak NLRP3 inhibitors include parthenolide, 3,4-methylenedioxy-β-nitrostyrene and dimethyl sulfoxide (DMSO), although these agents have limited potency and are nonspecific.

Current treatments for NLRP3-related diseases include biologic agents that target IL-1. These are the recombinant IL-1 receptor antagonist anakinra, the neutralizing IL-1β antibody canakinumab and the soluble decoy IL-1 receptor rilonacept. These approaches have proven successful in the treatment of CAPS, and these biologic agents have been used in clinical trials for other IL-1β-associated diseases.

There is a need to provide a compound with improved pharmacological and/or physiological and/or physicochemical properties and/or those that provide a useful alternative to known compounds. In particular, compounds with good activity and improved in-vitro stability.

Summary

In one aspect, the present disclosure provides a compound selected from

6-[[(3*R*)-1-ethyl-3-piperidyl]amino]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one; and

6-[[(3*R*)-1-ethyl-3-piperidyl]amino]-3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-4-methyl-1,2,4-triazin-5-one;

6-[[(3*R*)-1-Ethyl-3-piperidyl]-methyl-amino]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a compound as described herein for use as a therapeutically active substance.

In another aspect, the present disclosure provides a compound as described herein for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein and a therapeutically inert carrier.

In another aspect, the present disclosure provides the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

In another aspect, the present disclosure provides a compound as described herein for use in the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

In another aspect, the present disclosure provides a compound as described herein for use in the treatment or prophylaxis of a disease, disorder or condition selected from Alzheimer's disease and Parkinson's disease.

In another aspect, the present disclosure provides the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

In another aspect, the present disclosure provides the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Parkinson's Disease or Alzheimer's Disease.

In another aspect, the present disclosure provides an *in vitro* method of inhibiting NLRP3, which method comprises administering an effective amount of a compound as described herein to inhibit NLRP3.

Claims

1. A compound selected from

6-[[(3R)-1-ethyl-3-piperidyl]amino]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one;

6-[[(3R)-1-ethyl-3-piperidyl]amino]-3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-4-methyl-1,2,4-triazin-5-one;

6-[[(3*R*)-1-Ethyl-3-piperidyl]-methyl-amino]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein the compound is 6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one, or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein the compound is 6-[[(3R)-1-ethyl-3-piperidyl]amino]-3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-4-methyl-1,2,4-triazin-5-one, or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, wherein the compound is 6-[[(3R)-1-Ethyl-3-piperidyl]-methyl-amino]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one, or a pharmaceutically acceptable salt thereof.

5. A compound according to any of claims 1 to 4 for use as a therapeutically active substance.

6. A compound according to any of claims 1 to 4 for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

7. A pharmaceutical composition comprising a compound according to any of claims 1 to 4 and a therapeutically inert carrier.

8. The use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

9. A compound according to any of claims 1 to 4 for use in the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

10. A compound according to any of claims 1 to 4 for use in the treatment or prophylaxis of a disease, disorder or condition selected from Alzheimer's disease and Parkinson's disease.

11. The use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

12. The use of a compound according to any one of claims 1 to 4 in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Parkinson's Disease or Alzheimer's Disease.

13. An *in vitro* method of inhibiting NLRP3, which method comprises administering an effective amount of a compound as claimed in any one of claims 1 to 4 to inhibit NLRP3.